Antibodies as pharmacologic tools for studies on the regulation of energy balance

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OBJECTIVE: Active immunization in rats may serve several purposes: the production of a disease-like phenotype, the generation of pharmacologic tools, and the development of clinically useful therapies. We selected the melanocortin-4 receptor (MC4R) as a target because its blockade could provide a treatment for anorexia and cachexia. METHODS: We used a sequence of the N-terminal (NT) domain of the MC4R as an antigen. Rats immunized against the NT peptide produced specific MC4R antibodies (Abs) that were purified and characterized in vitro and in vivo. RESULTS: The Abs acted as inverse agonists and reduced under basal conditions the production of cyclic adenosine monophosphate in HEK-293 cells expressing the human MC4R. Rats immunized against the NT peptide developed a phenotype consistent with hypothalamic MC4R blockade, i.e., increased food intake and body weight, liver and fat-pad weights, hepatic steatosis, and increased plasma triacylglycerols. With a high-fat diet, plasma insulin levels were significantly increased. In separate experiments an increase in food intake was observed after injection of purified MC4R Abs into the third ventricle. When lipopolysaccharide was administered in NT-immunized rats the reduction of food intake was partly prevented in this model of cytokine-induced anorexia. CONCLUSION: Our results show that active immunization of rats against the MC4R resulted in the generation of specific Abs that stimulated food intake by acting as inverse agonists of the hypothalamic MC4R. Pharmacologically active monoclonal MC4R Abs could be the starting point for the development of novel treatments for patients with anorexia or cachexia.

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